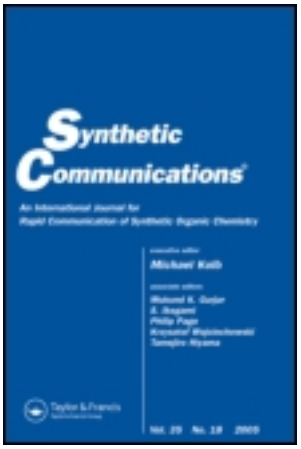

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 27 Dec 2013.

To cite this article: Xin Liu, Yu Liu, Huili He, Zhan Cai & Yushe Yang (2014) New Synthetic Route to (1S)-4,5-Dimethoxy-1-[(methylamino)methyl] Benzocyclobutane, a Key Intermediate of Ivabradine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:4, 451-456, DOI: 10.1080/00397911.2012.686081

To link to this article: http://dx.doi.org/10.1080/00397911.2012.686081

Synthetic Communications®, 44: 451–456, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.686081

NEW SYNTHETIC ROUTE TO (1S)-4,5-DIMETHOXY-1-[(METHYLAMINO)METHYL] BENZOCYCLOBUTANE, A KEY INTERMEDIATE OF IVABRADINE

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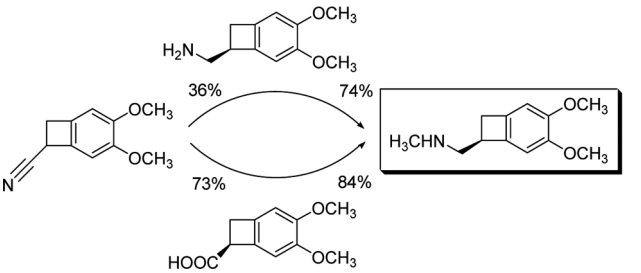
GRAPHICAL ABSTRACT



Abstract *An efficient process for the preparation of (1*S*)-4,5-dimethoxy-1-[(methylamino) methyl] benzocyclobutane (*S*)-**3** as ivabradine intermediate, which was obtained in 56% yield, is described. The salient feature of this process is the racemization of the undesired (1*R*)-4,5–dimethoxy-1,2-dihydrocyclobutabenzene-1-carboxylic acid (*R*)-**12**, and the overall yield of (*S*)-**12** was improved to 70% by three resolutions of the racemized acid with* R-(α)*-phenylethanamine. The reduction of amide (*S*)-**13** was achieved with $NaBH_4$-I_2 in refluxing tetrahydrofuran, giving the corresponding amine (*S*)-**3** in 90% yield. The improved synthetic route described herein is cost-efficient, environmentally friendly and feasibile for scale-up production.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Benzocyclobutane; ivabradine; reduction; resolution

Received October 9, 2011.

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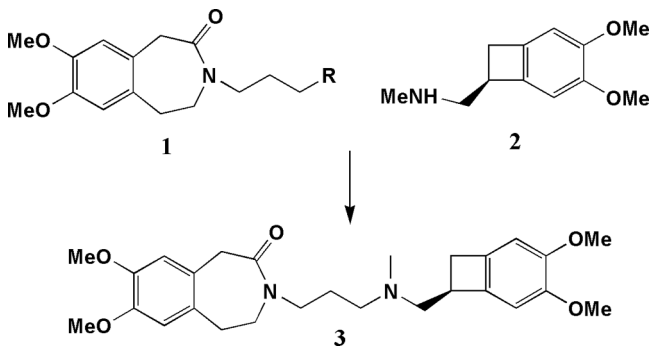
INTRODUCTION

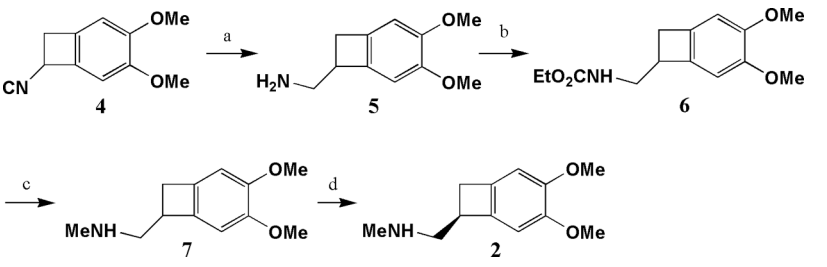
Ivabradine (**3**) is the first selective sinus node I*f* channel inhibitor for the treatment of stable angina pectoris, which was approved by the European Medicines Agency in 2005. It is specific for the I*f* current, lowering heart rate at concentrations that do not affect other cardiac ionic currents.[1–3] A commonly employed synthetic route to **3** (Scheme 1) involves the condensation of (1*S*)-N-[(4,5-dimethoxybenzocyclobut-1-yl)methyl]-N-(methyl)amine (**2**) with compound **1** (R=CHO, Cl or I) to afford the desired product,[4–8] thus making amine **2** an important intermediate for the preparation of ivabradine.

Two methods have been described for the preparation of **2**. The first one, reported in a patent,[9] started from (*R,S*)-1-cyano-4,5-dimethoxybenzocyclobutane **4** followed by three steps, namely reduction of the cyano group to **5**, acylation of **5** to **6**, and reduction of **6** with $LiAlH_4$.

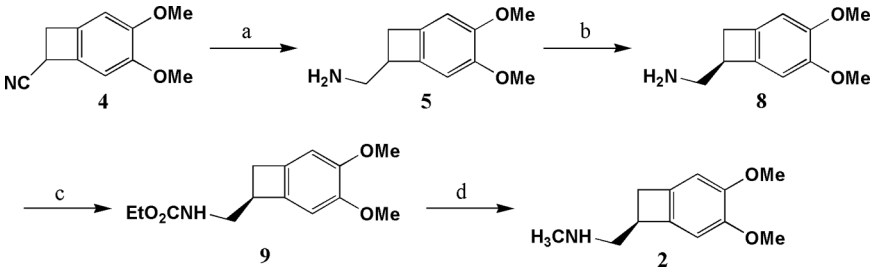
In the second method (Scheme 3),[10,11] amine **5** prepared by reduction of **4**, was resolved with N-acetyl-L-glutamic acid to produce the optical isomer **8**, followed by acylation of **8** with ethyl chloroformate to get **9** and reduction of **9** with $LiAlH_4$ to afford **2**. Although the yield of the resolution step was improved to 40%, the mother liquor from the resolution could not be racemized and recycled for use. Furthermore, an excess of $LiAlH_4$ (2–4 equiv) was required in reduction of **9**, which would leads to a large amount of waste in industrial production.



Scheme 1. Commonly employed synthetic route to ivabridine **3** to afford the racemate methylamine **7**. The resolution of **7** with *d*-camphorsulfonic acid gave **2** in only 5% yield (Scheme 2).



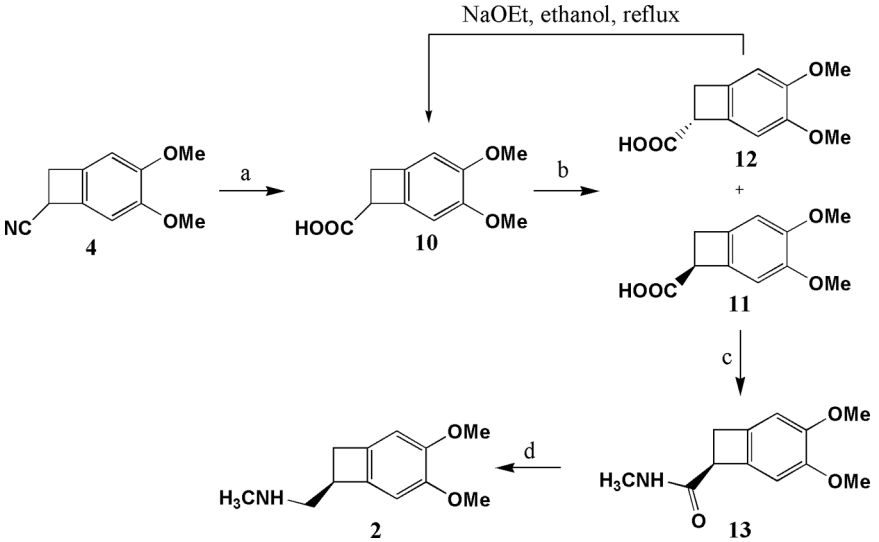
Scheme 2. (a) BH_3 complexed with THF, 90%; (b) ethyl chloroformate, Et_3N, DCM, room temperature, 80%; (c) $LiAlH_4$, THF, reflux, 92%; and (d) *d*-camphorsulfonic acid, 5%.



Scheme 3. (a) H_2/Raney Ni, THF, 60 °C, 30 bar; (b) (i) N-acetyl-L-glutamic acid, EtOH; (ii) NaOH aq., 40%; (c) ethyl chloroformate, Et_3N, CH_2Cl_2, 80%; and (d) $LiAlH_4$, THF, reflux, 93%.

To solve the problems mentioned and improve the resolution yield of amine **5**, we tried to racemize and recycle the "waste" isomer after resolution. Several bases, such as sodium ethoxide, potassium *tert*-butoxide, and *n*-butyllithium, were screened for racemization; however, no racemized amine **5** was obtained. Considering the fact that the commercially available cyano compound **4**[12] can be easily hydrolyzed to the carboxylic acid **10**, which can be treated with chiral resolution reagents to afford (−) isomer **11**, we decided to develop a new route based on carboxylic acid **10**. To optimize the racemization condition, sodium ethoxide, potassium *tert*-butoxide, and n-butyllithium were attempted.[13–15] To our delight, racemization of (+) isomer of **12** occurred smoothly by heating the mother liquor in the presence of sodium ethoxide, so the overall resolution yield of **11** is thus improved to 73%.

Thus our new procedure, illustrated in Scheme 4, proceeds via the facile hydrolysis of **4** with KOH in ethanol to give the carboxylic acid **10**. Dissolution of racemic **10** and *R*-(α)-phenyl ethylamine in hot *i*-PrOH followed by crystallization



Scheme 4. (a) KOH, EtOH, reflux, 95%; (b) (i) *R*-(α)-phenylethanamine, *i*-PrOH; (ii) 10% HCl, overall yield 70%; (c) ethyl chloroformate, $CH_3NH_2 \cdot HCl$, EtOH, THF, 93%; and (d) $NaBH_4/I_2$, THF, 90%.

at room temperature gave the salt of (−) isomer. The mother liquor thus formed was treated with sodium ethoxide for racemizatiom. The optical isomer **11** could be obtained in 73% overall yield through two resolutions. Compounds **11** reacted with ethyl chlorformate and methyl amine hydrochloride to afford **13** in 93% yield. $NaBH_4$-I_2 was used to replace $LiAlH_4$ in the reduction of **13** to give **2** in 90% yield.[16]

In conclusion, we have developed an efficient process to key intermediate **2**. The most excited step of this route is the racemization of **12**, which leads a good overall yield with simple workup and is cost efficient, environmentally friendly, and suitable for scale-up production.

EXPERIMENTAL

All reagents and solvents were commercially available and used without further purification unless otherwise stated. ^{1}H NMR spectra were recorded on a Bruker 300 NMR spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Electron impact–mass spectrometry (EI-MS) spectra were obtained on a Finnigan MAT 95 mass spectrometer. Elemental analyses were obtained using a Vario EL spectrometer. High-performance liquid chromatographic (HPLC) analysis and reaction monitoring were performed on Shimadzu SPD10AV liquid chromatograph equipped with a Chiralcel OD-H 250 mm × 4.6 mm 5-μM column; flow rate 0.5 mL/min, wavelength 230 nm, temperature 25 °C. The mobile phase for the HPLC analysis of **2** was done with hexane / isopropanol / trifluoroacetic acid (85:15:0.1).

(R,S)-4,5-Dimethoxy-1,2-dihydrocyclobutabenzene-1-carboxylic Acid (10)

A mixture of **4** (50.0 g, 0.26 mol) and KOH (250.0 g, 4.5 mol) in ethanol (1000 mL) was refluxed in a round-bottomed flask for 5 h. The reaction mixture was cooled to room temperature and then water (2500 mL) was added slowly into reaction flask until it became clear. Ethanol was evaporated off in vacuo, and the residue was acidified to pH 3 with concentrated HCl and extracted with ethyl acetate (500 mL × 3). The combined extract was dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The residue was washed with ethyl acetate (200 mL) to yield a white solid of **10** (52.0 g, 95%), mp 137–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (m, 2H), 3.85 (s, 6H), 4.25 (t, 1H, $J = 3.8$ Hz), 6.71 (s, 1H), 6.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 32.4, 46.2, 58.3, 114.5, 115.6, 127.7, 139.8, 148.5, 149.6, 178.6. EI-MS m/z 208 (M). Anal. calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.65; H, 6.01.

(*S*)-4,5-Dimethoxy-1,2-dihydrocyclobutabenzene-1-carboxylic Acid (11)

R-(α)-Phenylethanamine (28.8 g, 0.24 mol) was added dropwise in 30 min into solution of **10** (50.0 g, 0.24 mol) in isopropanol (500 mL). The mixture was refluxed for 1 h and allowed to crystallize at room temperature overnight. The white solid was collected and recrystallized from isopropanol three times, dissolved in water (125 mL), and acidified with 10% aqueous HCl to pH 2–3. The aqueous solution

was extracted with ethyl acetate (125 mL × 3). The ethyl acetate extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to afford **11** of 19.5 g (40% yield) as a colorless solid, mp 136–137 °C, $[\alpha]_D^{20} = -61$ (*c* 0.5, MeOH), *ee* = 99.4%.

The mother liquor from the crystallization was collected and concentrated. The residue was dissolved in water (125 mL) and acidified with 10% aqueous HCl to pH 2–3. The aqueous solution was extracted with ethyl acetate (125 mL × 3). The ethyl acetate layers were combined, dried over anhydrous Na_2SO_4, and concentrated to afford a solid (32.5 g). Sodium ethoxide (32.6 g, 0.48 mol) was added to an ethanol solution (250 mL) of the solid, and the mixture was stirred under refluxing for 8 h. After the reaction mixture was cooled to room temperature, water (250 mL) was added. The solvent was adjusted to pH 1–2 with 10% aqueous HCl. The aqueous solution was extracted with ethyl acetate (250 mL × 3), and the ethyl acetate layers were combined, dried over anhydrous Na_2SO_4, and concentrated to afford 32.5 g of the racemic acid **10**. The racemic acid **10** obtained from stage II was resolved following the workup described previously to give 11.4 g of **11** as a colorless solid (yield 22.8%, mp 135–137 °C, $[\alpha]_D^{20} = -60$ (*c* 0.5, MeOH), *ee* = 98.9%). Then the the mother liquor was also recycled as the procedure described previously and was resolved to give another 7.5 g of **11** as a colorless solid (yield 15.4%, mp 136–138 °C, $[\alpha]_D^{20} = -62$ (*c* 0.5, MeOH), *ee* = 98.8%). Finally an overall 38.4 g (76.8% yield) of **11** was obtained (*ee* = 98.9%). Mp 136–138 °C, retention time: 9.28 min, $[\alpha]_D^{20} = -60$ (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (m, 2H), 3.85 (s, 6H), 4.25 (t, 1H, *J* = 3.8 Hz), 6.71 (s, 1H), 6.77 (s, 1H). EI-MS *m*/*z* 208 (M). Anal. calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.50; H, 6.08.

(*S*)-(4,5-Dimethoxybenzocyclobut-1-yl)-N-(methyl)formamide (13)

Et_3N (9.6 g, 0.10 mol) was added to the solution of compound (*S*)-**11** (20.0 g, 0.10 mol) in THF (200 mL) in flask I, ethyl chloroformate (10.4 g, 0.10 mol) was added dropwise, and the resulting mixture was stirred for 20 min at room temperature. Another portion of Et_3N (29.3 g, 0.29 mol) was added to a solution of methyl amine hydrochloride (20.0 g, 0.29 mol) in THF (120 mL)/H_2O (80 mL) in flask II and stirred for 10 min. The mixture in flask II was dropped into the solution in flask I and reacted for another 20 min. Water (300 mL) was added to the residue after THF was removed in vacuo, and the aqueous solution was extracted with ethyl acetate (200 mL × 3). The extract was washed with 1 N aqueous HCl, aqueous $NaHCO_3$, and brine successively, dried over Na_2SO_4, and then concentrated to afford (*S*)-**13** (20.0 g, 93%, *ee* = 98.0%). Mp 144–146 °C, retention time: 16.67 min, $[\alpha]_D^{20} = -31.2$ (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (d, 3H, *J* = 4.8 Hz), 3.15 (d, 1H, *J* = 13.6 Hz), 3.50 (dd, 1H, *J* = 13.6 Hz, 5.5 Hz), 3.87 (d, 6H, *J* = 3.3 Hz), 4.10 (m, 1H), 6.75 (d, 2H, *J* = 2.9 Hz). EI-MS *m*/*z* 221 (M). Anal. calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.95; H, 6.71; N, 6.25.

(1*S*)-4,5-Dimethoxy-1-[(methylamino)methyl]benzocyclobutane (2)

A solution of iodine (46.0 g, 0.18 mol) in THF (200 mL) was added dropwise to a stirred suspension of $NaBH_4$ (15.0 g, 0.40 mol) and **13** (30.0 g, 0.14 mol) in THF (300 mL) at 0–5 °C. The resulting mixture was stirred under reflux for 24 h before

it was cooled to 0 °C, and then carefully quenched by addition of 1 N aqueous HCl 500 mL. After neutralization with 1 N NaOH, the mixture was concentrated. H_2O (300 mL) was added to the residue, and the aqueous solution was extracted with ethyl acetate (200 mL × 3). The organic layer was combined and dried over Na_2SO_4, and the product **2** was obtained as a white solid by removal of the solvent without further purification (25.6 g, 90%, *ee* = 99.1%). Retention time: 18.14 min, $[\alpha]_D^{20} = -27.2$ (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.76 (d, 1H, $J = 13.4$ Hz), 2.88 (m, 2H), 3.25 (dd, 1H, $J = 13.4$ Hz, 4.9 Hz), 3.58 (m, 1H), 3.85 (s, 6H), 6.71 (d, 2H, $J = 5.6$ Hz). EI-MS m/z 207 (M). Anal. calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.45; H, 8.25; N, 6.65.

ACKNOWLEDGMENT

We are grateful to Nanjing C&O Pharmaceutical Technology (Holdings) Limited for the support of this research.

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